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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/805,761	03/13/2001	Parkash S. Gill	VASG-PO3-003	4201

28120 7590 04/20/2005
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EXAMINER

MCGARRY, SEAN

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/805,761

Applicant(s)

GILL ET AL.

Examiner

Sean R. McGarry

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 January 2005.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 8-11, 14 and 19-21 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-4, 8-11, 14 and 19-21 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/18/04 and 1/21/05 have been entered.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4, 8-11 and 14 remain and new claims 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uchida et al [US 6,150,092] in view of Robinson [WO 95/04142, cited by applicant], Agrawal et al [PNAS Vol. 94: 2620-2625, 1997, cited by applicant] and Bennett et al [US 5,998,148].

Uchida et al have taught antisense and pharmaceutical compositions comprising antisense targeted to VEGF. Uchida et al have also taught the inhibition of VEGF in a subject via antisense nucleic acids targeted to VEGF (see claims 18-25, for example). In particular Uchida et al have taught antisense targeted to SEQ ID NO: 7 of VEGF and have taught numerous specific oligonucleotides targeted to SEQ ID NO: 7 such as SEQ ID NOS:49, 50, 51, 54, 53, 50, 49, 38, and 41 (see claims 1-16, for example). It has

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been taught by Uchida et al that inhibition of VEGF results in the inhibition of solid tumor growth (see column 1, for example) and have taught that if VEGF is present in the tumor it is subject to VEGF inhibitory treatment. It has been taught that the development of antisense oligonucleotides to VEGF replaces the methodology of inhibiting VEGF in tumors with antibodies (see column 2, for example). Columns 4-5 discuss how one in the art can use known oligonucleotide modifications in VEGF antisense oligonucleotides, for example. At columns 7-8 it is taught that various kinds of cancer can be treated with VEGF directed antisense molecules. At column 27 it has been taught that VEGF antisense oligonucleotides can be used to inhibit the growth of solid tumors via the inhibition of VEGF which inhibits angiogenesis which in turn inhibits the growth of solid tumors, for example.

The antisense oligonucleotides claimed by Uchida et al are targeted, for example, to the specific region of VEGF nucleic acid SEQ ID NO: 7. It is noted that antisense oligonucleotides of the instant application, including claimed SEQ ID NO: 34 (modified version of SEQ ID NO: 2) as well as SEQ ID NOS: 2, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 28, and 29, for example, are all targeted to SEQ ID NO: 7 of Uchida et al, and further all the antisense oligonucleotides of the instant application either overlap, embrace, or are embraced by the specifically claimed antisense of Uchida et al claim 7, for example (SEQ ID NOS: 49, 50, 51, 54, 53, 50, 49, 138, and 141 of Uchida et al, for example). It is clear that the antisense oligonucleotides claimed by Uchida et al reasonably be expected to have an IC₅₀ value of between about 0.5 and 2.5 micromolar, especially since the claims (i.e. 4, 5, 12, 13) do not require any

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particular conditions to ascertain an IC50 value, for example. Finally Uchida et al have taught that that region of VEGF SEQ ID:7 is a "core region" (see column 21-22) and further teach at column 26 that "[I]n view of the role of VEGF as a tumor angiogenic factor in vivo [citations omitted], the antisense nucleic acid having a nucleic acid sequence complementary to 8 or more nucleotides in the core region is useful as a therapeutic agent such as anticancer drug to inhibit the growth of solid tumors or a diagnostic agent for cancers." Uchida et al have taught at columns 4-9 that phosphorothioate –type oligonucleotides are preferable and act as substrate for RNaseH. At columns 8-9 it has been taught to use liposomes to facilitate the delivery of antisense oligonucleotides to cells in culture and to cells in an animal.

Uchida et al do not teach the 2'O-methyl modifications of SEQ ID NO: 34, the specific cells of claim 7, or chemotherapeutic agents included in a composition comprising a VEGF antisense.

Robinson et al have taught the inhibition of VEGF to inhibit tumor angiogenesis (see page 4, for example). It has been taught at pages 7-8 that modifications to antisense nucleic acids are desirable to prevent attack by nucleases, for example. It has been taught specifically, at pages 8-9, for example, the modification of an antisense oligonucleotide to comprise oligonucleotides that comprise an unmodified internal sequence that is flanked on the 5' and 3' termini by modified nucleic acid sequences.

Agrawal et al have taught the same modification used in SEQ ID NO: 34 in Table 1, for example. It has been taught that this oligonucleotide has nuclease resistance, for example.

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Bennett et al have taught many available modifications available to one in the art at the time the invention was made and this includes hybrid, mixed and gapmer oligonucleotides which all relate to an antisense oligonucleotide comprising an RNase substrate region (which includes phosphorothioate linkages) between modified portions of an oligonucleotide, where the modification(s) provide for increased nuclease protections and/or better substrate affinity, for example (see columns 6-10 and particularly Example 5, for example). At columns 12-13 it has been taught the numerous available compositions and delivery vehicle available for one in the art at the time of invention including the use of liposome formulations for the delivery of antisense oligos to a patient, for example.

One in the art would clearly have had motivation to make the instantly claimed antisense molecules since it is absolutely clear that the region targeted (core region SEQ ID NO:7 of Uchida et al) has been clearly shown by the prior art to be a desired target for antisense inhibition of VEGF where Uchida et al have taught that one in the art would expect antisense oligonucleotide so targeted to inhibit VEGF in solid tumors. Furthermore the specific antisense is not only targeted to the taught target sequence but overlaps, embrace or are embraced by the specific VEGF antisense taught by Uchida et al where the instant application has shown that antisense targeted thereto would be expected to have an IC50 value recited in the claims (ie the IC50 value is an observed property of antisense targeted to this core region of VEGF, for example).

[A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION, AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFTS TO THE APPLICANT TO SHOW AN UNOBVIOUS DIFFERENCE]

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“[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency’ under 35 U.S.C. 102, on prima facie obviousness’ under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted].” The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).]

One in the art would clearly look to this specific region to make antisense oligonucleotides to inhibit VEGF since this specific region and antisense thereto have been clearly taught in the art to be effective antisense oligonucleotides and target sequence. One would expect that the inhibition conditions recited in the claims would be met since these values were observed upon making antisense targeted to the specific region clearly taught in the prior art. One would have been motivated to make the modification specifically as in instant SEQ ID NO: 34 since this type of modification was clearly taught in the art as one of many modifications one in the art could choose to increase nuclease stability or to increase target affinity, for example. Bennett et al have clearly shown that liposome delivery is one of a number of methods one in the art could have chosen to deliver an antisense to a subject. One would clearly have chosen any of the vast range of solid tumors where VEGF is expressed since it is clear from the teachings of Uchida et al and Robinson that any tumor expressing VEGF is clearly a target for antisense VEGF therapy. In regard to claims 2, 3, the following is noted:

“It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art.” *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of

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preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie* obvious.). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held *prima facie* obvious). But see *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been *prima facie* obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive....Appellant argues... hindsight reconstruction or at best,... obvious to try'.... We agree with appellant.").

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Applicant's arguments filed 1/21/05 and 6/18/04 have been fully considered but they are not persuasive. The declaration of Parkash Gill, filed 6/18/04 is

considered in this Official Action, but the weight of the evidence presented therein is of insufficient weight to overcome the rejection of record.

Applicant argues essentially as was argued in the After Final response filed 6/18/04 and further comprises arguments that assert that the claims presently pending pertain only to antisense oligonucleotides that are modified for use in cells or *in vivo*. Although the compound claims may have compounds that may be used in *in vivo* applications their use is not necessarily limited thereto, but the art does provide motivation, teaching and expectation of success in using VEGF antisense in cells and *in vivo*.

Applicant argues that according to the declaration of Dr Gill, the cited art which provides dozens of antisense probes that are effective at suppressing VEGF expression in a cell free assay (see paragraph 5 of the declaration). Dr Gill then opines that the oligonucleotides are not effective in cell culture without providing any evidence that would show support for such a conclusion (see paragraph 6 of the declaration). It is noted that the declaration points to Tables 8 and 9 of Uchida et al. where it was asserted by Uchida et al that the results show that the phosphorothioate oligonucleotides are effective in cells. Note at column 24, lines 63-64 it is stated that phosphorothioate oligonucleotides that provide from VEGF expression between 8% and 57% were considered to be effective. Also note that oligonucleotides 51 and 138 which overlap with the instant SEQ ID NO: 34 showed expression levels of 56% and 41% respectively. It appears that the declaration of Dr. Gill presents a difference of opinion without any evidence to show that the assertions of Uchida et al are not true.

Both applicants' arguments and the declaration seem to assert that the oligonucleotides of Uchida were not meant for in vivo use (see paragraph 4 of the declaration). It is noted that Uchida et al have shown that phosphorothioate antisense oligonucleotide function in cells and further that phosphorothioate oligonucleotides are preferred in their invention. It is further noted that oligonucleotides such as SEQ ID NO: 49, 50 and 51 of Uchida are specifically claimed in a method of treating a subject (see claim 20, for example, and also methods of treating a subject with antisense targeted to SEQ ID NO: 7 are claimed.

Applicant argues that the question at issue is not what the examiner would conclude from a review of the prior art but what one of ordinary skill would conclude from a review of the prior art, and what modifications to the prior art one of ordinary skill in the art would be motivated to make. Applicant asserts that the declaration of Dr. Gill provides evidence of what a practitioner in the field would be motivated to do based on the basis of Uchida et al. It is the examiner's position that the declaration provides an opinion. If applicant believes there are material facts present in the declaration they are invited to point to them with particularity.

Applicant argues that the Uchida reference does not teach the specific sequence SEQ ID NO: 34 with the specific modifications of SEQ ID NO: 34 and the added limitation of new claims 19-21. Applicant argues that there is no motivation from Uchida et al or the other prior art references to make the invention as claimed. The examiner's arguments of record are relied upon here since applicant's arguments are substantively the same as those presented throughout the prosecution of this application. A quick

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diagram of the target region and the antisense of Uchida in relation to the instant SEQ ID NO: 34 is provided to show the context of the examiner arguments. SEQ ID NO: 7 and 49-51 are from Uchida, SEQ ID NO: 49 and 50 provided 100% inhibition and SEQ ID NO: 51 provided 96% inhibition under the conditions of Uchida et al. SEQ ID NO: 7 is shown in 3'-5' orientation.

CCTACCGAACTTCTACATGAGCTAGAGTAGTCCCATGAGGAC	7
UGGCTTGAAGATGTACTCGAU	34
AAGATGTACTCGATCTCATC	49
GGCTTGAAGATGTACTGGAT	50
CGGATGGCTTGAAGATGTA	51

It should be noted that SEQ ID NO: 50 of Uchida differs by only one nucleotide from SEQ ID NO: 34 and that the specific region targeted by SEQ ID NO: 34 has been completely blanketed by antisense oligonucleotides that has great inhibitory capacity. Further, it is noted that none of this is new argument as these specific sequences have been pointed to repeatedly throughout the prosecution of the instant application. It is clear that one would have chosen this particular region to target for antisense compounds for use in inhibition of VEGF expression. The region is clearly shown to be an effective target and the instant inventions sequence differs by only one nucleotide from a specific sequence known in the art to be quite effective. That nucleotide not included in the specific sequence (of SEQ ID NO: 50) is included in another effective antisense oligonucleotide known in the art to be quite effective (SEQ ID NO: 51). Applicant has offered no reason or evidence to show any unexpected properties of the instantly claimed antisense oligonucleotide but only offers that maybe the antisense of

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the prior art will not work well in an in vivo environment if modified. No evidence to support this assertion is provided. Applicant argues that one would only modify antisense if they were intended to be used in cells. Well, the claims of Uchida et al are clearly drawn to methods of inhibition of VEGF *in vivo*. Clearly the antisense oligonucleotides are intended for cellular use. The Other prior art references relied upon all teach the use of antisense oligonucleotides as therapeutics, and further Robinson et al and Uchida et al specifically teach the use of Anisense oligonucleotides targeted to VEGF as therapeutics. Applicant argues that it would be unclear that 2'O-methyl-modifies oligonucleotides would be effective in cells unless there is evidence. Well, again the prior art provides that such modifications (2'-O-methyl modifications) are used to provide enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. This point is important since applicant appears to believe, that since the use of phosphorothioate modified antisense in cells showed less inhibition than unmodified antisense in cell free assay indicates that one would not use such modifications in practice. This is a flawed argument. The modification provides protection from nucleases where they are present. If one uses non-modified antisense in cells they are more prone to nuclease degradation and thus is the very reason such modifications are used where nucleases are present. The environment of a cell is much more degradative to an antisense due to the presence of nucleases, for example. Applicant has attempted to use modifications and data that is associatively related and make it causatively related. Applicant has provided no evidence, such as a side by side comparison of the Uchida oligonucleotides (SEQ ID NOS: 549, 50 and 51, which are

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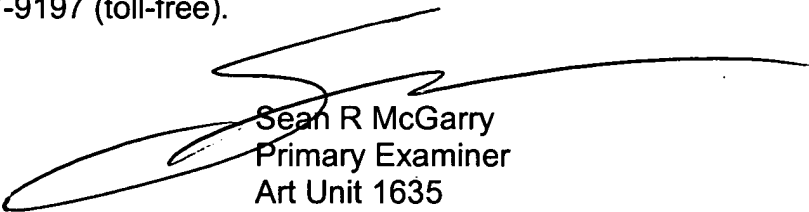
most closely related to SEQ ID NO: 34) in the targeted region, and shown that the oligos of the prior art would not function as the teachings of both the Agrawal and Bennett reference teach that they would with the same modification of SEQ ID NO: 34. Both the Agrawal and Bennett references have taught that it is beneficial in therapeutic antisense applications to use 2'-O-methyl modifications. Applicant should note that the specific Example 5 pointed to in Bennett et al is directed to those same 2'-O-methyl modifications claimed (including the newly added limitation of including a phosphorothioate linkage, for example). The disclosure of both of these references make it clear that one would chose such a modification (See columns 6-10 of Bennett et al for example) for therapeutic applications, for example. The prior art, taken as a whole, clearly teaches the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Sean R McGarry
Primary Examiner
Art Unit 1635

SRM